REMARKS

Claim Amendments

By this amendment Claim 43 has been rewritten so that it no longer depends upon Claim 33 and no longer is subject to rejection or objection for "reciting noncorresponding method steps. (Office Action, Item 21). Claim 43 likewise is no longer subject to the new ground of rejection that it is "multiply dependent" (O.A., Item 45). It is believed that Claim 43, as now amended, is free of the rejections set out in Items 21 and 45 of the action. Claims 45 has also been amended.

Claim 50 has been revised in an effort to clarify that it covers the preprepared immunochromatographic device available from Applicants' assignee for the purpose of conducting the immunochromatographic test embodiment of the present invention employing the purified antigen-specific antibodies of his invention.

Claims 52-54 have been cancelled, thereby obviating the rejections of Item 22 of the action.

Response to Prior Art Item 23 of the Action

In regard to the term "antigen-specific" as used herein, it is requested that the Examiner consider its meaning in the way that Applicants have used it in their specification. As so contemplated, for example, Imrich *et al*, which identifies *no particular* antigen anywhere in its disclosure and claims, does *not* describe or refer to *any* kind of "antigen-specific" antibodies. *Every* bacterium to which Imrich *et al*, refers is known to include plurality of

antigens. Imrich *et al* in stating, e.g. that "Group A Streptococcus in pharyngeal exudates can be identified" (Col. 1, lines 55-57) identifies *no particular* antigen and in no way suggests that detection can be made more surely or readily by targeting a *particular* antigen among those that a particular bacterium (including the Group A *streptococcus* bacterium mentioned) possesses.

In the context of "antigen-specific antibodies" as used in Applicants' specification, the emphasis is upon the *specific* ability of the antibodies in detecting a *particular* antigen, in this case the C-polysaccharide cell wall antigen that is present in all strains and serotypes of *Streptococcus pneumoniae*. The point here is that Applicants' antigen-specific antibodies, as obtained by passing polyclonal antibodies to *Streptococcus* bacteria over the chromatographic affinity column to which the purified C-polysaccharide cell wall antigen of *S. pneumoniae* has been coupled through a spacer molecule, all as described in Applicants' application, have a *specific affinity* for *S. pneumoniae* C-polysaccharide cell wall antigen, whether it is still contained in the bacterium in its natural state or it has been freed from the bacterium, e.g. by the treatment that occurs when the bacterium is passed through the kidneys of an infected human being. It is this specific affinity for the specific named antigen of *S. pneumoniae* that has imparted to Applicants' FDA-approved immunoassay the sensitivity and specificity that inspired the FDA to grant its first approval, ever, to a rapid test for the diagnosis of disease caused by *Streptococcus pneumoniae*. The prior standard test require culturing bacteria from sputum (or another sample of bodily fluid or exudate)e for up to a week and then examining the culture under a microscope to identify the bacterium believed to be causing the disease.

This FDA approval of Applicants' assay and the fact that the approved assay can be conducted in 20 minutes, enabling *immediate* disease diagnosis, caused the approval, which occurred shortly after the September 1999 filing of this application, to be featured in newspaper, television and radio reports for several days after it was announced.

In the sense of *specific affinity*, Applicants acknowledge that Imrich *et al* do teach, for some of the bacteria mentioned, using monoclonal antibodies and that monoclonal antibodies do have specific affinities for the particular antigens they are capable of detecting. Having said that, however, it remains Applicants' position that, contrary to item 34 of the action, Imrich *et al* does *not* teach antibodies *specific* to any particular antigen of *Streptococcus pneumoniae*.

This can clearly be seen in Imrich *et al* Claim 15 which covers "The device of claim 10, [wherein] the immunoglobulin is specific for microbial antigen of.." a list of names of bacteria each followed by the word "antigen". Careful reading shows that there is no identification in that claim of any *particular* antigen of *Streptococcus pneumoniae* or any other bacterium. Furthermore, Imrich *et al* do not even identify any *particular* monoclonal antibody, it being well-known in the art that a monoclonal antibody always has *specific affinity* for *only* one antigen.

Applicants further dispute the implication of item 30 of the action that what Imrich *et al* says about Group A or Group B *streptococcus* assays is suggestive of, or necessarily even pertinent, to arriving at an assay that will show whether or not *Streptococcus pneumoniae* is present in a particular patient sample by identifying a *particular* antigen characteristic of the bacterium.

The rejection repeated in item 23 of the action that claims 50-51 are obvious under 35USC 103(a) over Imrich *et al* in light of Gribnau *et al* in view of Krook *et al* is again traversed herein. The fact is that these references as a group *do not* lead to Applicants' claimed invention. While Imrich *et al* do show a cumbersome immunochromatographic process involving various combined or alternative sample pretreatments that are neither necessary nor desirable to the preprepared immunochromatographic device of claims 50 and 51, Imrich *et al* do not show any method involving detection in a patient sample of a *particular antigen* characteristic of a specific disease-causing bacterium. Gribnau *et al* shows use of gold as a labelling agent for detection of antibody-antigen reactions. Applicants do not contend they invented the use of gold as a labelling agent, and it is specifically referred to in Claim 51 only because it is an ingredient of the specific immunoassay that the FDA approved which Applicants' assignee manufactures and sells.

Krook *et al* does show an assay for the C-polysaccharide cell wall antigen of *Streptococcus pneumoniae*, but it differs markedly from Applicants' assay in that it requires two different antibodies–one monoclonal and one said to be "affinity-purified". The assay is an ELISA test requiring "approximately 2 hr." (p.73) to complete. By contrast, Applicants' immunochromatographic assay requires *the same* antigen-specific antibodies to "sandwich" the antigen on *both sides* and is completed within 20 minutes from the application of the sample to the preprepared immunochromatographic strip.

No matter *how* the Examiner combines Imrich *et al*, Gribnau and Krook, the "subject matter as a whole" of Applicants' claim 50 or, alternatively, its dependent claim 51, does not result. Yet 35 U.S.C.§103(a), under which the rejection is advanced, *requires* that "the

differences between the subject matter sought to be patented and the prior art" be such "that the *subject matter as whole* would have been obvious at the time the invention was made to a person having ordinary skill in the art". (35U.S.C.§103(a), emphasis added)

In this regard, it was not intended to assert that the Examiner relied upon Sjogren *et al* in making the §103(a) rejection made in the preceding office action. The point intended to be made, and perhaps ineptly asserted, was simply that the two-site ELISA test for the C-polysaccharide cell wall antigen of *S. pneumoniae* employing one monoclonal antibody and one polyclonal, allegedly "affinity purified", antibody was developed at the Karolinska Institute in Stockholm by a group of researchers all working together, various members of which published articles between 1985 and 1987 on this "two site" assay. This group included *at least* Krook, Holmberg, Sjogren and Holme. A person of ordinary skill in the art, wanting to understand fully what they did, would be motivated to consult all of their articles and--faced with the fact that the Krook & Holmberg article relied on by the Examiner does not describe the "affinity" purification procedure used for the polyclonal antibody, would naturally go to publications of others in the group relating to the "two-site ELISA" assay to find out what those articles say on the subject. Such a person would immediately find reference in Sjogren (cited by the Examiner) a description of a "purification" method *different* from that of Applicants and *not* likely to result in identical antibodies to those obtained by Applicant's methodology.

The Rejection of Claims 50 and 51
As Set Forth In Item 24 Of The Action Is Traversed

In a real sense, Claim 50 or, alternatively, dependent Claim 51, each express the *same invention* as that set forth in the allowed claims, but in the form of a *product* embodiment rather than as a process.

As already noted, these claims cover the FDA-approved product in which the also FDA-approved assay of the allowed claims is to be performed. The antigen-specific antibodies, which make the assay work in the particular way that it does to identify within 20 minutes the cell wall C-polysaccharide antigen of *S. pneumoniae*, if present, in a liquid sample are movably deposited in the first zone of the ICT strip and immovably deposited as a stripe in the second zone where the antigen is "caught" in a sandwich between the one increment of movable antibody labelled with gold (or another label) and a second increment of the same antibody that is *im*movable and *un*labelled.

The antigen-specific antibodies of this invention are not the same as either of Krook's monoclonal antibody or Krook's "affinity-purified" antibody. Their ability to react with each target antigen twice to make a "sandwich" shows that each antibody has two determinants that bind to the antigen.

While Applicants do not contest that their assay *could* be performed in the May device *if* that device were prepared as Claim 50, or, alternatively, Claim 51 requires, this does not render Applicant's prepared device containing an ICT strip *the same* as what might be obtained by combining Krook's two-site assay employing two different antibodies and the May device. Here again, the "subject matter as a whole" of Applicants' invention is simply *not* suggested

by any combination of the Mays and Krook references that can be made.

Furthermore, the fact that Krook, viewed by itself, shows using *two different* antibodies to detect the same antigen does not and cannot detract from the patentability of and the inventiveness of, applicant's use of two increments of the same antibody, *different from either* of those employed by Krook, to detect the C-polysaccharide antigen of *S. pneumoniae* that is the goal of both Krook and applicants.

A new and unobvious way of attaining a result formerly obtained in a different way *is* a patentable invention.

It is noted that May, like Imrich *et al,* does *not*, at page 17, line 10 or elsewhere, purport to identify any particular *antigen* of "Streptococcus" to be identified and it is again noted that bacteria, normally have multiple antigens. Moreover, *Streptococcus* A, B, C and D are each different organisms from *Streptococcus pneumoniae* and from one another, and the mere mention of any or all of them in the May patent does not signify *anything* with regard to the patentability of Claims 50 and 51. This is because these claims address ICT device prepared to perform an assay for a *specific* antigen *only*.

The Examiner in Item 46 of the Action misapprehends the thrust of Applicants' having pointed out in answer to the last action that the device which is preprepared as defined in claims 50 and 51 was not *itself* invented by them and asks what have they invented and whether the claim is a Jepsen claim. Applicants' intention in making the statement was to draw a distinction between (1) the *naked device* which, in fact, is a mere mechanical association of appropriate components including a housing and an ICT strip, and is not adapted to perform any *particular* assay and (2) the device as *prepared* for conducting a specific assay

as defined in claims 50 and 51. The device as preprepared for the conduct of a particular assay, as in Claims 50 and 51, is an article new in the art as compared to the device alone and has its own specific use that the naked device as invented by others is not capable of performing.

As stated earlier, claims 50 and 51 which define the preprepared device simply state Applicants' invention in a product format rather than a process format. This alternative form of claim is appropriate because these preprepared devices are the major component of kits for the detection of the C-polysaccharide cell wall antigen which is characteristic of all serotypes of *Streptococcus pneumoniae* and Applicants' assignee is entitled to a claim that covers them.

CONCLUSION

With the claim amendments herein made, claims 43-47, 50 and 51 are believed to be allowable. Early action to that effect is courteously requested.

Respectfully submitted,

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43. A method of detecting the presence of the cell wall C-polysaccharide antigen of *Streptococcus pneumoniae*, in a liquid sample, which method comprises the following steps:

a) culturing *Streptococcus pneumoniae* bacteria, to obtain a desired size of culture and harvesting therefrom cells thereof as a wet cell pellet;

b) separating from the wet cell pellet the cell wall C-polysaccharide containing not more than 10% protein by performing a series of steps which comprises;

(i) suspending the wet cell pellet in an alkaline solution and mixing;

(ii) adjusting the pH to an acid pH with a strong acid;

(iii) separating the mixture from step (ii) into two layers;

(iv) removing the upper layer and adjusting its pH to approximate neutrality;

(v) adding to the product from step (iv) a broad spectrum protease enzyme and digesting to destroy residual proteins;

(vi) adjusting the pH of the product from step (v) to an alkaline pH with a weakly alkaline aqueous solution; and

(vii) separating out the cell wall C-polysaccharide antigen containing not more than 10% protein;

c) coupling to a chromatographic column through a spacer molecule the cell wall C-polysaccharide antigen containing not more than 10% protein

obtained in step (b);

d) passing polyvalent antibodies to *Streptococcus pneumoniae* over the chromatographic affinity column of step (c) to produce purified antigen-specific antibodies; and

[The method of Claim 42 in which step (e) is conducted by contacting]

e) conducting an immunoassay upon a liquid sample suspected of containing *Streptococcus pneumoniae* and/or its free cell wall C-polysaccharide antigen, by a method which comprises the steps of:

(i) contacting the sample with the sample-receiving end of a strip of bibulous material, which strip is contained within an ICT device comprising a housing and itself comprises at least two zones, specifically

[i] (A) a first zone in which has been movably embedded a conjugate of a labelling agent with purified antigen-specific antibodies obtained in step (d) [of Claim 33] hereof, said labelling agent being selected from among those which manifest a visible color change upon the formation of a labelled antibody-antigen-fixed antibody reaction product; and

[ii] (B) a second zone having fixedly bound thereto a stripe of unconjugated purified antigen-specific antibodies from step (d) [of Claim 33] hereof, which zone is equipped with

a view window in the [housing] ICT device for viewing the appearance of a color characteristic of the massing of the labelling agent upon the formation of the labelled antibody-antigen-fixed antibody reaction product;

[b] (ii) allowing said liquid sample to flow laterally along said [test] strip of bibulous material, to said first zone where it picks up said [the] movably embedded conjugate of a labelling agent with antigen-specific antibodies from [obtained in] step (d) hereof, [of Claim 33]

[c] (iii) allowing said liquid sample and said conjugate of a labelling agent with antigen-specific antibodies from step (d) hereof to flow laterally together along said [test] strip of bibulous material to said second zone and [while] concomitantly [reacting to form labelled antibody-antigen conjugates with] allowing any C-polysaccharide cell wall antigen of *Streptococcus pneumoniae* present in the sample, whether in free or combined form, to react with said conjugate to form labelled antibody-antigen conjugates and

[d] (iv) within not more than 20 minutes after [first] contacting [the liquid] said sample with [the test strip] said strip of bibulous material, observing through said view window in [the housing] said ICT device whether a line of color has formed, which line of

color is indicative of the massing of said [label] labelling agent along [the] said stripe of unconjugated antigen-specific antibodies from step (d) hereof, which massing takes place as labelled antibody-antigen-fixed antibody reaction products are formed [.] and signifies the presence in the sample of the C-polysaccharide antigen of *Streptococcus pneumoniae*.

45. The method of claim 44 wherein the sample is selected from among human urine and human sputum.

50. An immunochromatographic ("ICT") [ICT] device for the detection of the C-polysaccharide cell wall antigen of *Streptococcus pneumoniae* in a liquid sample, which device comprises a housing containing a strip of bibulous material, which strip of bibulous material has at least

a). a first zone in which has been movably embedded a conjugate of a labelling agent and [purified] antibodies specific to the cell wall C-polysaccharide antigen of *Streptococcus pneumoniae* and

b). a second zone, downstream of said first zone [which zone is] and equipped with a window in the housing [for viewing a line of color along said stripe,] to which second zone is immovably bound a stripe of antibodies specific to the cell wall C-polysaccharide antigen of *Streptococcus pneumoniae*; [which color is indicative of the massing of the labelling agent along the immovably bound stripe as a consequence of the formation of labelled antigen-antibody-immovable antibody

sandwiches, whereby a line of color denotes the presence in the liquid sample of the C-polysaccharide cell wall antigen of *Streptococcus pneumoniae;*]

wherein all of [which] said antibodies specific to the cell wall C-polysaccharide antigen of *Streptococcus pneumoniae* in both zones [are further characterized in that their antigen specificity has been attained] have been obtained by passing polyvalent antibodies to *Streptococcus pneumoniae* over a chromatographic affinity column to which is coupled a spacer molecule conjugated to a purified cell wall C-polysaccharide antigen of *Streptococcus pneumoniae* obtained from a culture of *Streptococcus pneumoniae* according to a [the following] method comprising the steps of:

(i) harvesting [bacterial] cells from the said culture in the form of a wet cell pellet;

(ii) suspending the wet cell pellet in an alkaline solution and mixing;

(iii) adjusting the pH of the resultant mixture to an acid pH with a strong acid;

(iv) separating the acidified product from step (iii) into two layers;

(v) removing the upper layer and adjusting its pH to approximate neutrality;

(vi) adding to the product from step (v) a broad spectrum protease enzyme and digesting to destroy residual proteins;

(vii) adjusting the pH of the product from step (vi) to an alkaline pH with a weakly alkaline aqueous solution: and

cell wall C-polysaccharide antigen of *Streptococcus pneumoniae* having no more than 10% protein.